

# Travel-Associated Dengue Illnesses Among Wisconsin Residents, 2002-2008

Mark J. Sotir, PhD, MPH; Diep K. Hoang Johnson, BS; Jeffrey P. Davis, MD

## ABSTRACT

**Introduction:** Dengue infections in humans can result in self-limited illness or conditions that can be severe and life-threatening. Persons traveling to many tropical regions are at risk for dengue infection. This report retrospectively summarizes travel-associated dengue cases occurring among Wisconsin residents from 2002 through 2008.

**Methods:** We used a surveillance case definition based on the Centers for Disease Control and Prevention (CDC) 1996 dengue illness case definition. Detection of dengue-specific IgM antibody in serum specimens was used for laboratory confirmation of dengue. Clinical and travel histories, mosquito exposure, and repellent use were obtained from patients by interview using arbovirus-specific data collection forms.

**Results:** During 2002-2008, 32 travel-associated dengue illnesses were reported among Wisconsin residents; none met the case criteria of dengue hemorrhagic fever or dengue shock syndrome. Fever (100%), headache (90%), and myalgia (87%) were the most frequently reported signs and symptoms. Nine (28%) patients were hospitalized; no deaths occurred. Onsets in 25 (81%) of 31 patients with reported travel histories occurred after return to Wisconsin. Eighteen (56%) of the 32 patients were female; median age was 35.5 years (range 12 to 68 years). Patients most frequently reported travel to Mexico/Central America (45%) or the Caribbean Islands (39%). Cases occurred during all months. Reported mosquito exposure was high among patients (85%), but consistent repellent use was low (6%).

**Conclusions:** Dengue illnesses occur in travelers to dengue-endemic tropical areas. Travelers to these areas must take precautions to prevent mosquito bites. Clinicians should consider dengue in travelers who develop febrile illnesses with headache or myalgia within 2 weeks of their return. Arboviral diseases, including dengue, are reportable in Wisconsin.

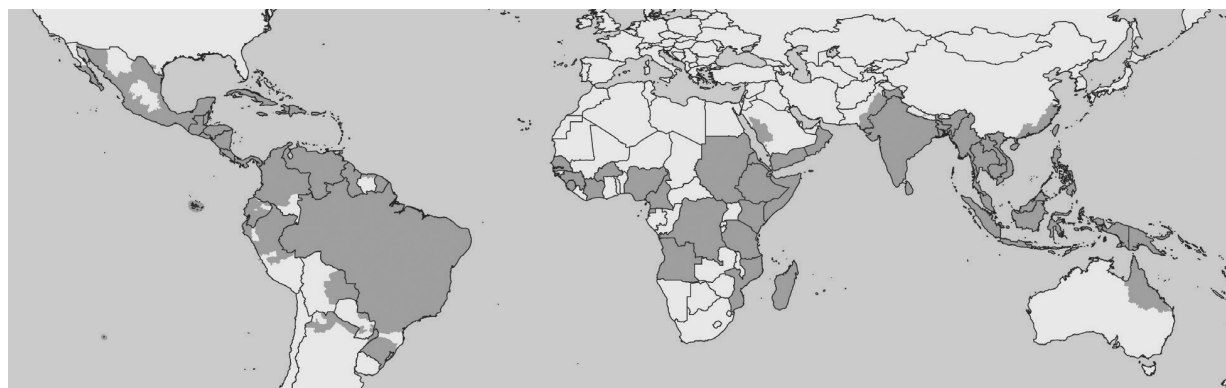
## INTRODUCTION

Dengue virus is a flavivirus, a genus of viruses that include West Nile virus and yellow fever virus.<sup>1</sup> Dengue virus has 4 distinct serotypes (Dengue 1, 2, 3, and 4) that are almost always transmitted to humans from the bite of an *Aedes* mosquito, typically *Aedes aegypti*.<sup>2</sup> The spectrum of dengue illness in humans ranges from self-limited dengue fever (DF) illness, typically consisting of sudden onset of fever, headache, myalgia, and rash, to dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS), conditions that can be severe and life-threatening.<sup>1,3</sup> The incubation period for dengue illness is typically 4-7 days (range: 3-14 days), with fever lasting from 2 to 7 days.<sup>1</sup>

Dengue is endemic throughout tropical areas of the world, including Mexico and Central America, the Caribbean, South America, the Indian subcontinent, Indonesia, Africa, and Australia and New Zealand (Figure 1). Dengue endemicity is increasing worldwide because of the vast and increasing range of its primary vector, the *Aedes aegypti* mosquito.<sup>5</sup> This geographic expansion began following World War II<sup>1</sup> and has been dramatic during the past 20 years.<sup>5</sup> Dengue virus is unique among arboviruses because it is fully adapted to the human host and the human environment, virtually eliminating the need for a primitive enzootic forest cycle and other animal reservoirs to ensure its maintenance.<sup>2</sup> Although not endemic within the United States mainland, dengue is well-established in Puerto Rico,<sup>3</sup> and dengue infections have recently been documented among US residents who live near the Texas-New Mexico border.<sup>6</sup>

**Author Affiliations:** Bureau of Communicable Diseases, Wisconsin Division of Public Health, Madison, Wis (Sotir, Johnson, Davis); Division of Foodborne, Bacterial and Mycotic Diseases, Centers for Disease Control and Prevention, Atlanta, Ga (Sotir).

**Corresponding Author:** Mark J. Sotir, PhD, MPH, Mail Stop A-38, Enteric Diseases Epidemiology Branch, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Atlanta, GA 30333; phone 404.639.1547; e-mail MSotir@cdc.gov.



**Figure 1.** Distribution of dengue in the western and eastern hemispheres.<sup>4</sup>

Travel-associated dengue infections are documented worldwide,<sup>5,7-8</sup> including among US citizens.<sup>9-11</sup> These reports illustrate the continuing risk of dengue infection among persons travelling to tropical regions where dengue is endemic. Periodic dengue epidemics, such as those occurring in the Caribbean and Brazil in 2007 and 2008,<sup>12</sup> increase the risk to travelers who visit such areas when epidemics are occurring.

This report retrospectively summarizes reported travel-associated dengue cases occurring among Wisconsin residents from January 2002 through December 2008. We describe epidemiologic and clinical characteristics of case patients, document the locations of patient travel, examine the seasonality of cases, assess mosquito exposure and repellent use among case-patients during their exposure-related travel, and provide recommendations to reduce the risk of dengue infection while travelling.

## METHODS

### *Case Definition*

We used the Centers for Disease Control and Prevention (CDC) 1996 dengue illness case definition<sup>13</sup> as a basis for the surveillance case definition used to classify dengue illnesses occurring in Wisconsin residents. Dengue illness was defined as an acute febrile illness with an associated positive immunoglobulin M (IgM) antibody test of an acute or convalescent serum to any 1 of the 4 dengue viruses in a person with recent travel to a dengue-endemic area and with onset from January 1, 2002 through December 31, 2008. DHF was defined as dengue illness with minor or major bleeding phenomena, thrombocytopenia ( $\leq 100,000/\text{mm}^3$ ), and evidence of plasma leakage documented by hemoconcentration (hematocrit increased by  $\geq 20\%$ ) or other objective evidence of increased capillary permeability. DSS was

defined as dengue illness that met the definition for DHF with hypotension or narrow pulse pressure ( $\leq 20$  mm Hg). DF was defined as dengue illness not meeting the criteria for DHF or DSS.

### *Laboratory Testing*

Laboratory confirmation of dengue infection in all patients was obtained by testing acute serum specimens. Testing for the presence of dengue-specific IgM antibody using enzyme-linked immunosorbent assays (ELISAs) was conducted at 6 different commercial laboratories within the continental United States; for 1 patient, similar testing was conducted at the CDC laboratory in San Juan, Puerto Rico. Laboratory staff forwarded dengue IgM-positive laboratory results to the Wisconsin Division of Public Health (WDPH) and WDPH staff subsequently reported these results to the local health department (LHD) of jurisdiction. The Wisconsin State Laboratory of Hygiene (WSLH) does not routinely confirm positive dengue-IgM results from commercial laboratories.

### *Epidemiologic Data Collection and Analysis*

Patient data were obtained by LHD or WDPH staff during routine surveillance follow-up after laboratory reports of positive IgM ELISA tests to 1 of the 4 dengue virus serotypes were received by the WDPH. Data on demographic features, illness onset date, clinical signs and symptoms, hospitalization, and recent travel history ( $\leq 14$  days prior to illness onset) were obtained using standardized data collection forms, either the WDPH Arbovirus Infection Follow-up Form or the CDC Dengue Case Investigation Form. Mosquito exposure/bite data (mosquito exposure and bites, mosquito exposure only, neither mosquito exposure nor bites) and frequency of repellent use while traveling (always, most of the time, sometimes, or never) were collected

for patients with onsets during 2006 through 2008. Data were entered into a Microsoft Excel database and quantitative analyses were conducted using Epi Info software, version 3.3.2 (CDC, Atlanta, GA).

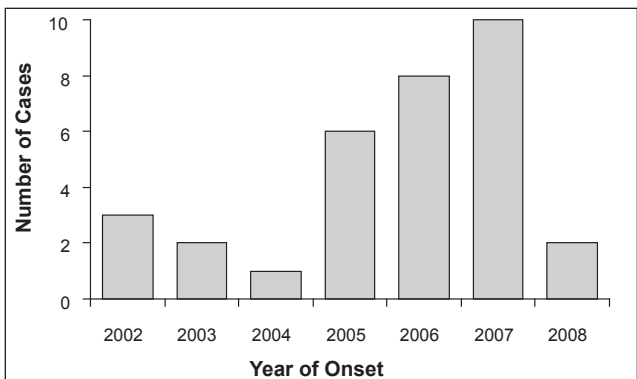
## RESULTS

From January 1, 2002 to December 31, 2008, 32 reported cases of travel-associated dengue illness occurred among Wisconsin residents who visited dengue-endemic areas; 24 (75%) cases occurred during 2005-2007 (Figure 2). All cases were classified as DF; no DHF or DSS were reported. Cases occurred in residents of 15 Wisconsin counties: Brown (2), Calumet (1), Columbia (1), Dane (9), Jefferson (2), Kenosha (1), La Crosse (2), Marathon (1), Marinette (1), Milwaukee (5), Outagamie (2), Pierce (1), Sheboygan (1), Winnebago (2), and Wood (1). Median age of case patients was 35.5 years (range 12-68 years); 18 (56%) were female.

Laboratory confirmation of dengue infection was determined serologically for all case patients. All but 1 serum specimen was obtained within 60 days of symptom onset (median=8 days, range 1-59 days); 1 specimen was collected 161 days following symptom onset. Specimens for 26 (81%) of the 32 patients were obtained at least 6 days after onset, with 17 (65%) of the 26 collected between 6 and 14 days after onset. Of the 31 patients with travel history, 25 (81%) had both symptom onset and confirmatory specimen collection after returning to Wisconsin, 5 (16%) had onset overseas but confirmatory specimen collection in Wisconsin, and 1 (3%) had onset and confirmatory specimen collection in Puerto Rico.

Clinical information was reported for 31 cases (Table 1). As typically reported among patients with DF illness, fever (100%), headache (90%), and myalgia (87%) were the most frequently reported signs or symptoms. Rash was reported in 14 (45%) patients. Two patients reported petechiae and 1 reported hematuria, but none of these patients had illnesses meeting the DHF case definition. One patient, a 60-year-old man with onset in 2008, reported a previous dengue infection in 1969. Nine (28%) patients were hospitalized; length of hospitalizations ranged from 1 to 5 days (median 3 days). No deaths occurred.

Information on travel before illness onset was available for 31 patients. Dengue infection for most patients occurred in dengue-endemic parts of Mexico/Central America (45%) or the Caribbean Islands (39%) (Table 2). The specific travel destinations most frequently reported by patients were Mexico (6), Puerto Rico (4), and Costa Rica (4). Other areas of exposure included



**Figure 2.** Travel-associated dengue cases (n=32) among Wisconsin residents by year of illness onset, January 1, 2002 to December 31, 2008.

**Table 1.** Prevalence of Reported Signs and Symptoms Among Wisconsin Residents with Travel-Associated Dengue Illnesses With Onsets from January 1, 2002, to December 31, 2008

Sign/Symptom	Case Patients Reporting n (%) <sup>a</sup>
Fever	31 (100)
Headache	28 (90)
Myalgia	27 (87)
Fatigue	22 (71)
Nausea	16 (52)
Arthralgias	14 (45)
Rash	14 (45)
Diarrhea	12 (39)
Vomiting	9 (29)
Photophobia	8 (26)
Eye Pain	6 (19)

<sup>a</sup> n=31; no clinical information was available for 1 patient. Petechiae, backache, and tremors were each reported by 2 patients. Dizziness, backache, stiff neck, disorientation, night sweats, joint swelling, and blood in urine were each reported by 1 patient.

the Indian Subcontinent, Southeast Asia, South America, the South Pacific Islands, and the Arabian Peninsula. Onsets of travel-related dengue illness among Wisconsin residents occurred throughout the entire calendar year (Figure 3).

Mosquito exposure and bite data during the 14 days before illness onset were available for 20 patients. Seventeen (85%) of the 20 patients reported mosquito exposure with bites, 2 (10%) reported exposure with no bites, and 1 (5%) reported neither exposure nor bites. Of the 18 patients with repellent use information, 7 (39%) reported that they never used repellent, 7 (39%) indicated sometimes using repellent, and 3 (17%) reported using repellent most of the time; only 1 (6%) patient reported always using repellent during travel before illness occurrence.

**Table 2.** Travel Destinations by Dengue-Endemic Area for 31 Wisconsin Residents with Travel-Associated Dengue Illnesses With Onsets from January 1, 2002 to December 31, 2008

Dengue-Endemic Geographic Region and Country	No. of Cases Linked to Region <sup>a</sup>
Mexico/Central America	14
Mexico	6
Costa Rica	4
Honduras	3
Nicaragua	2
El Salvador	1
Guatemala	1
Caribbean Islands	12
Puerto Rico	4
Dominican Republic	2
Trinidad	1
Martinique	1
Haiti	1
Antigua	1
St. Lucia	1
Grenada	1
Indian Subcontinent	2
India	1
Pakistan	1
Southeast Asia	2
Thailand	1
Laos	1
South America	1
Brazil	1
South Pacific Islands	1
Chuuk (Truk) Island	1
Arabian Peninsula	1
Saudi Arabia	1
Africa	1
Nigeria	1
Australia	0

Note: Travel destination information missing for 1 patient.

<sup>a</sup> During the 14 days before illness onset, 2 patients traveled to both Caribbean Islands and Central America and 1 patient traveled to the Arabian Peninsula and Indian Subcontinent.

## DISCUSSION

Dengue is now the most common arboviral infection in the world;<sup>14</sup> at least 2.5 billion people worldwide live in areas where dengue is transmitted.<sup>1-2</sup> This report documents recent travel-associated dengue infections among Wisconsin residents and demonstrates that Wisconsin residents who travel to dengue-endemic areas are at risk for dengue illness. Most of the ill travelers were infected while visiting destinations geographically proximal to the continental United States, particularly in the Caribbean or Central America. Nearly half of these patients with dengue visited the popular vacation destinations of Mexico, Puerto Rico, or Costa Rica within 2 weeks of illness onset. However, cases were also documented in patients who travelled to most of the other

dengue-endemic areas, including South America, Africa, Arabia, the Indian Subcontinent, Southeast Asia, and the South Pacific Islands.

Clinical presentation of dengue among patients described in this report was typical of DF. Fever was reported for all patients, and headache, myalgias, and fatigue were each prominently reported; rash and gastrointestinal signs and symptoms were reported less frequently. Other than petechiae being reported in 2 patients, there was no evidence of DHF or DSS in the Wisconsin patients, likely in part because only 1 patient reported a previous dengue infection. While all patients included in this report had non-hemorrhagic dengue illnesses, 28% were ill enough to require hospitalization.

Laboratory confirmation of infection is required for diagnosis of dengue. Diagnoses are made by detecting virus in acute phase blood or serum (obtained <6 days after illness onset),<sup>15-16</sup> or detecting specific antibodies in convalescent specimens (obtained ≥6 days after onset) typically using an IgM capture ELISA test<sup>16</sup> in persons with clinical illness and travel histories consistent with dengue infection. IgM usually appears at detectable levels within 6 to 7 days after onset of illness and can persist up to 60 days or more.<sup>17</sup> To confirm the diagnosis, serological testing of paired acute and convalescent sera for 4-fold difference in titers in IgM or IgG is recommended.<sup>15</sup> This is especially important in testing patients residing in dengue-endemic countries.<sup>18</sup> ELISA testing for anti-dengue virus IgM and IgG antibody is available in most commercial and reference laboratories. A real-time reverse transcription (RT)-PCR testing for dengue virus RNA able to detect specific serotypes is also available in some commercial laboratories.<sup>19</sup>

ELISA tests detecting anti-dengue IgM can be limiting because of their inability to differentiate between the 4 specific dengue virus types and cross-reactivity may occur with other flaviviruses.<sup>15,18</sup> However, a positive IgM titer from a single specimen can be useful for surveillance and diagnosis of dengue virus infection when epidemiologic information and clinical signs and symptoms are available and consistent with acute infection.<sup>20</sup> Most of the Wisconsin patients that were positive for IgM antibodies to dengue virus were obtained at least 6 days after illness onset, and available clinical symptoms and travel history to endemic-dengue areas supported the diagnosis of dengue virus infection.

Onsets of dengue illnesses occurred during all months among these patients, suggesting that clinical suspicion of dengue in returning travelers should be year-round. However, overall risk for dengue is not uniform, but seasonal, and can depend on the endemic-

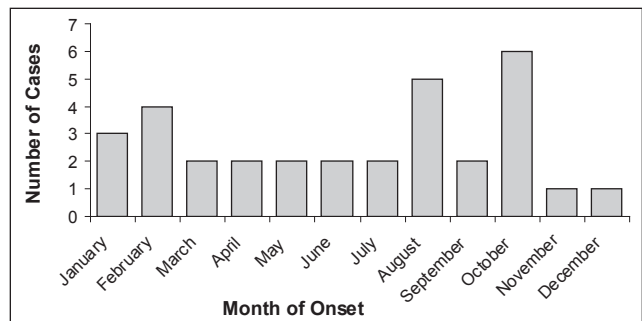
ity and seasonal conditions in the areas visited.<sup>5,12,21</sup> For example, dengue cases in Puerto Rico and other areas in the Caribbean region generally increase from May to November due to increases in rainfall,<sup>21</sup> with the highest number of travel-associated cases between August and December.<sup>5</sup> Epidemics of dengue might also depend on additional weather factors, including global warming, which might change conditions that affect both dengue endemicity and epidemicity.<sup>21</sup>

*Aedes aegypti* is most frequently found in or near human habitats and prefers to feed on humans during daytime hours.<sup>22</sup> Alarming, repellent use among patients during travel was infrequent or non-existent among patients, despite mosquito bites being frequently reported. Only 1 of 18 patients with repellent use information reported using insect repellents consistently during travel. Because the majority of Wisconsin patients acquired dengue infections in destinations close to the United States, it is possible they were unaware or unconcerned by the risk of mosquito-borne infections in these places.

Risk of severe illness is markedly higher in persons who have existing dengue antibodies acquired by previous infection or passively from their mother before birth.<sup>23-24</sup> Studies have indicated antibody against dengue virus after infection can be long-lived, as much as 30 to 45 years or maybe even longer.<sup>25</sup> However, presence of antibodies of 1 dengue serotype (Dengue 1, 2, 3, 4) provides no long-term cross protection against dengue viruses of the other 3 serotypes and instead leaves the person at greater risk for DHF or DSS if he or she becomes subsequently infected with dengue virus of a different serotype.<sup>1,25</sup> Co-circulation of multiple dengue serotypes, or hyperendemicity, now occurs in many areas of the Americas and Southeast Asia and places those areas at increased risk for higher community-wide rates of severe dengue illnesses.<sup>1</sup>

All arboviral diseases are reportable in Wisconsin. Reporting of dengue illnesses in Wisconsin is conducted as part of a laboratory-based statewide arbovirus surveillance program, with laboratories required to report positive dengue tests to the WDPH. Clinicians are also required to report confirmed and suspected cases of dengue to the local health department where the patient lives. This dual reporting is important in ensuring that dengue illnesses are reported to the WDPH, which subsequently reports them to the CDC.

In 2001, following introduction of West Nile virus (WNV) into the state, arboviral-related surveillance was enhanced when federal funds were provided to the WDPH, WSLH, and LHDs to support WNV-related



**Figure 3.** Travel-associated dengue cases (n=32) among Wisconsin residents by month of illness onset, January 1, 2002 to December 31, 2008.

laboratory and epidemiologic activities. The enhancements likely improved the detection and reporting of all arboviral infections, including dengue, to the WDPH. This might also partly explain why most of the cases in this report occurred during 2005–2007. However, factors such as economic conditions and increased foreign travel during that time might also be important.

## RECOMMENDATIONS AND CONCLUSION

The risk of dengue among travelers is increasing and not likely to decrease in the near future. We recommend that all travelers to dengue-endemic areas be educated about the risk of dengue, including receiving recommended pre-travel advice on dengue illness by a knowledgeable health care professional.<sup>8</sup> Travelers should use precautions designed to reduce mosquito exposure, including remaining in well-screened or air-conditioned areas if possible, wearing clothing that covers arms and legs, and applying an effective insect repellent (such as one containing DEET) to skin and clothing.<sup>22</sup>

Clinicians need to consider dengue in returning travelers who have onset of a febrile illness with headache or myalgias within 2 weeks of returning from a tropical or subtropical area where dengue viruses may be present. Patients with dengue infections should be made aware that whenever they travel to dengue-endemic areas in the future, they will be at greater risk of experiencing more serious illness if they are infected with a dengue virus of different serotype. Travelers previously infected with dengue virus should consider avoiding mosquito exposure, especially during peak transmission times, when in areas where dengue is transmitted,<sup>5</sup> and be educated on recognizing the warning signs of severe dengue illness (ie, cool and clammy skin, petechiae, rapid pulse, lethargy or restlessness, bleeding gums, abdominal pain, or persistent vomiting) especially if

they occur 24 hours before or after defervescence.<sup>1</sup> If such signs or symptoms should occur, patients should seek medical attention immediately.

Finally, since dengue and other arboviral infections continue to occur in Wisconsin residents, reporting of these infections to the public health system should continue. This reporting is vital to arboviral surveillance in Wisconsin and the United States.

**Acknowledgments:** We thank clinicians and laboratorians for reporting the cases of dengue in this manuscript to the Wisconsin Division of Public Health. We also acknowledge D. Fermin Arguello, MD, Dengue Branch, Centers for Disease Control and Prevention, for reviewing and providing context to some of the information contained in this report.

**Funding/Support:** None declared.

**Financial Disclosures:** None declared.

## REFERENCES

- Gubler DJ. Dengue and dengue hemorrhagic fever. *Clin Microbiol Rev.* 1998;11:480-496.
- Gubler DJ. The global emergence/resurgence of arboviral diseases as public health problems. *Arch Med Res.* 2002;33:330-342.
- Rigau-Perez JG, Laufer MK. Dengue-related deaths in Puerto Rico, 1992-1996: diagnosis and clinical alarm signals. *Clin Infect Dis.* 2006;42:1241-1246.
- Centers for Disease Control and Prevention. Traveler's Health—Yellow Book: Other Infectious Diseases Related to Travel. <http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-5/dengue-fever-dengue-hemorrhagic-fever.aspx>. Accessed December 1, 2009.
- Schwartz E, Weld LH, Wilder-Smith, et al. Seasonality, annual trends, and characteristics of dengue among ill returned travelers, 1997-2006. *Emerg Infect Dis.* 2008;14:1081-1088.
- Ramos MM, Mohammed H, Zielinski-Gutierrez E, et al. Epidemic dengue and dengue hemorrhagic fever at the Texas-Mexico border: results of a household-based seroepidemiologic survey, September 2005. *Am J Trop Med Hyg.* 2008;78(3):364-369.
- Wilder-Smith A, Schwartz E. Dengue in Travelers. *N Engl J Med.* 2005;353:924-932.
- Lindback H, Lindback J, Tegnell A, Janzon R, Vene S, Ekdahl K. Dengue fever in travelers to the tropics, 1998 and 1999. *Emerg Infect Dis.* 2003;9:438-442.
- CDC. Travel-associated dengue infections—United States, 2001-2004. *MMWR.* 2005;54:556-558.
- CDC. Travel-associated dengue—United States, 2005. *MMWR.* 2006;55:700-702.
- Rigau-Perez JG, Gubler DJ, Vorndam AV, Clark GG. Dengue: a literature review and case study of travelers from the United States, 1986-1994. *J Travel Med.* 1997;4:65-71.
- CDC. Outbreak Notice. Update: Dengue, tropical and subtropical regions. <http://www.cdc.gov/travel/contentDengue-TropicalSubTropical.aspx>. Accessed November 30, 2009.
- CDC. Dengue fever (dengue hemorrhagic fever) 1996 case definition. [http://www.cdc.gov/ncphi/diss/nndss/print/dengue\\_fever\\_current.htm](http://www.cdc.gov/ncphi/diss/nndss/print/dengue_fever_current.htm). Accessed November 30, 2009.
- Wilder-Smith A, Chen LH, Massad E, Wilson ME. Threat of dengue to blood safety in dengue-endemic countries. *Emerg Infect Dis.* 2009;15:8-11.
- Wichmann O, Stark K, Shu PY, et al. Clinical features and pitfalls in the laboratory diagnosis of dengue in travelers. *BMC Infect Dis.* 2006;6:120.
- Dengue and dengue hemorrhagic fever: Information for health care providers. <http://www.cdc.gov/ncidod/dvbid/dengue/dengue-hcp.htm>. Accessed November 30, 2009.
- Dengue fever. In Heymann DL (ed.). *Control of Communicable Diseases Manual*. 19th Ed. Washington, DC: American Public Health Association; 2008:164-168.
- Hunsperger EA, Yoksan S, Buchy P, et al. Evaluation of commercially available anti-dengue virus immunoglobulin M tests. *EID.* 2009;15:436-440.
- Munoz-Jordan JL, Collins CS, Vergne E, et al. Highly sensitive detection of dengue virus nucleic acid in samples from clinically ill patients. *J Clin Microbiol.* 2009;47:927-931.
- Vaughn DW, Green S, Kalayanarooj S, et al. Dengue in the early febrile phase: viremia and antibody responses. *J Infect Dis.* 1997;176:322-330.
- Jury MR. Climate influence on dengue epidemics in Puerto Rico. *Int J Environ Health Res.* 2008;18(5):323-334.
- CDC. Health information for international travel, 2010. Chapter 5: Other infectious diseases related to travel. Dengue fever (DF) and dengue hemorrhagic fever (DHF). Tomashek KM (ed). <http://www.cdc.gov/travel/yellow-book/2010/chapter-5/dengue-fever-dengue-hemorrhagic-fever.aspx>. Accessed November 30, 2009.
- Halstead SB, Nimmannitya, Cohen SN. Observations related to pathogenesis of dengue hemorrhagic fever. IV. Relation of disease severity to antibody response and virus recovered. *Yale J Biol Med.* 1970;42:311-328.
- Burke DS, Nisalak A, Johnson DE, Scott RM. A prospective study of dengue infections in Bangkok. *Am J Trop Med Hyg.* 1988;38:172-180.
- Vaughn DW, Green S, Kalayanarooj S, et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. *J Infect Dis.* 2000;181:2-9.